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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

	Thomas Dag Horn and Sandra Marchese Johnson	Examiner: Yu, Misook
Serial No.:	10/081,185	Group Art Unit: 1642
Filed:	February 25, 2002	Docket: 110.004US2
For:	IMMUNOTHERAPY OF EPITHELIAL TUMORS USING INTRALESIONAL INJECTION OF ANTIGENS THAT INDUCE A DELAYED TYPE HYPERSENSITIVITY REACTION	

TRANSMITTAL LETTER FOR

APPELLANTS' AMENDED BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In response to the Communication Re: Appeal mailed August 4, 2006, I am transmitting the following with this transmittal letter.

Appellants' Amended Brief on Appeal.

Return postcard.

By: Hugh McTavish Date: Aug. 18, 2006

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Hugh McTavish

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APPELLANTS' AMENDED BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Amended Brief is presented in support of the Appeal filed August 24, 2005, from the final rejection of claims 1, 4-7, 15, 33, 36, 37, and 48-51 of the above-identified patent application, as set forth in the Final Office Action mailed May 31, 2005.

This Amended Brief is submitted in reply to the Communication Re: Appeal mailed August 4, 2006. An original Brief was filed on August 24, 2005, accompanied by a Notice of Appeal and a check in the amount of $500 to cover the small entity fees for Notice of Appeal and filing a brief in support of an appeal under 37 C.F.R. § 41.20(b)(1) and (b)(2). A previous Amended Appeal Brief was submitted on December 2, 2005.

APPELLANTS' BRIEF ON APPEAL

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1. REAL PARTY IN INTEREST

The real party in interest of the above-identified patent application is the assignee, the Board of Trustees of the University of Arkansas, Little Rock, AR.

2. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences known to Appellants' representative that will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

3. STATUS OF CLAIMS

Claims 1, 4-7, 9-12, 15-17, 33, 36-37, 40-41, and 46-51 (Appendix I) are pending in this application. Claims 9-12, 16-17, 40-41 and 46-47 stand withdrawn from consideration as drawn to a non-elected invention. Claims 1, 4-7, 15, 33, 36-37, and 48-51 stand rejected and are the subject of this appeal.

The claims withdrawn from consideration are incorrectly not listed as pending in the Examiner's Final Office Action. These claims were never cancelled and so are still pending. It is the appellants' position that claim 1 is a linking claim with respect to the withdrawn claims, and thus if claim 1 is found allowable, the withdrawn claims, which include all of the limitations of the linking claim, must be rejoined.

4. STATUS OF AMENDMENTS

The claims have not been amended since the final rejection.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The invention involves intralesionally injecting antigens that cause a cutaneous delayed type hypersensitivity reaction into epithelial tumors such as warts, thereby causing a cutaneous delayed type hypersensitivity immune response in the area of the wart. The invention is based on the discovery that even when the antigens are not related to the virus that causes warts, the antigen injection leads to the production of immune cells that recognize the virus causing the wart, and the immune cells then reduce the severity of warts, including warts distant from the site

where the antigen was administered, or cure the patient of warts. (Specification, pages 5-6, paragraphs 16-17; page 16, Table B.)

Independent claim 1 recites a pharmaceutical composition comprising at least two antigens and a pharmaceutically acceptable carrier, wherein (1) each of said antigens induces or is capable of inducing a cutaneous delayed type hypersensitivity response in a mammalian subject; (2) the composition is capable of treating a benign epithelial tumor caused by a papilloma virus in a mammalian subject; and (3) one of the two antigens is a bacterial antigen and the other is a candida antigen. Claim 1 is supported, e.g., by originally filed claims 1, 3, 8, and 9; at pages 5-6, paragraphs 16-17; the Example at pages 12-17; Table B at page 16; page 12, paragraph 36, line 3 of the paragraph; pages 12-13, paragraph 39, lines 3-4 of the paragraph; page 13, paragraph 39, lines 15-17 of the page; and page 9, paragraph 27, line 3 of the page.

Claim 15 is supported, e.g., by originally filed claim 15; at paragraphs 30 and 32 on pages 10-11.

Claim 48 is supported, e.g., by originally filed claim 1; and at page 9, paragraph 27, lines 6-8 of the page; and page 5, paragraph 16, lines 8-9 and 12-14 of the paragraph.

Claim 49 is supported, e.g., by originally filed claim 1; and page 9, paragraph 27, line 4 of the page.

Claim 50 is supported, e.g., by originally filed claim 1; and at page 5, paragraph 16, lines 4-6.

Claim 51 is supported, e.g., by originally filed claim 1; and at page 9, paragraph 27, lines 3-6 of the page.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

a. Whether claims 1, 4-7, 33, 36, and 48-51 are anticipated by Bostwick, E. (U.S. Published Patent Application 2002/0009429 A1) under 35 U.S.C. § 102(e) in spite of a declaration that, as the Examiner concedes, establishes possession of the invention of administering antigens causing a delayed type hypersensitivity response to epithelial tumors to treat the tumors, including antigens unrelated to the causative agent of the epithelial tumor, before the effective date of Bostwick.

b. Whether claims 1, 4-7, 33, 36-37, and 48-51 are anticipated under 35 U.S.C. 102(e) by Clements (U.S. Patent No. 6,033,673) under a theory of inherency.

c. Whether claims 1, 4-7, 15, 33, 36-37, and 48-51 are obvious under 35 U.S.C. § 103(a) over Clements or Bostwick in further view of the Candin package insert.

For each ground of rejection which appellant contests herein that applies to more than one claim, such additional claims, to the extent separately identified and argued below, do not stand or fall together. In particular, under ground of rejection (b), claims 48-51 are each argued separately.

7. ARGUMENT

Issue (a) – Whether claims 1, 4-7, 33, 36, and 48-51 are anticipated by Bostwick, E. (U.S. Published Patent Application 2002/0009429 A1) under 35 U.S.C. § 102(e) in view of a declaration that, as the Examiner concedes, establishes possession of the invention of administering antigens causing a delayed type hypersensitivity response to epithelial tumors to treat the tumors, including antigens unrelated to the causative agent of the epithelial tumor, before the effective date of Bostwick.

The Examiner rejected claims 1, 4-7, 33, 36, and 48-51 under 35 U.S.C. § 102(e) as anticipated by Bostwick (U.S. Published Patent Application 2002/0009429 A1, filed January 29, 1999). This rejection is respectfully traversed.

In a Declaration under 37 C.F.R. § 1.131 dated 11/8/04 and filed with the response on 11/19/04 the inventor Dr. Horn states that he conceived the claimed invention of the present application before the filing date of Bostwick and diligently pursued development from conception until the filing of the patent application. The declaration of prior conception is evidenced by an attached approval letter dated before January 29, 1999, "to proceed with use of mumps and candida intradermal skin test antigens to treat human patients afflicted with Verruca vulgaris (common warts)." Dr. Horn goes on to note:

> The letter refers to the use of mumps and candida antigens. At the time of the letter, I also believed that any antigen that induced a cutaneous delayed-type hypersensitivity response, including bacterial antigens, would successfully treat warts and other benign epithelial tumors. At the time of this letter from Dr. Faas and at the time of submitting the protocol that the letter refers to, I planned to combine two or more antigens in a single composition to be administered for treatment of warts and other epithelial tumors. The compositions with two or more antigens that I had conceived and planned to use included compositions containing mumps and candida antigens, as well as compositions containing candida and bacterial antigens.

The Examiner asserts that this only "establishes conception of a composition comprising mumps and candida antigens to treat . . . common warts," (Office Action mailed Feb. 2, 2005) but does not establish conception of a composition comprising candida and bacterial antigens, each of which induces or is capable of inducing a cutaneous delayed type hypersensitivity reaction.

Appellants disagree. The declaration establishes conception of a composition containing any antigen or antigens that induce or are capable of inducing a cutaneous delayed type hypersensitivity reaction to treat common warts. Common warts are caused by human papilloma virus (HPV) (specification, page 1, lines 19-20), not by either candida or mumps. This was obviously understood by Dr. Horn when he planned to use candida and mumps antigens to treat warts. Candida is a fungus and mumps is a virus, so the two antigens have little in common other than both having a high prevalence of reactivity in humans that results in the elicitation of a DTH response (specification, page 5, lines 5-7). It strains credulity to argue that when Dr. Horn planned to use candida and mumps antigens, which he knew were unrelated to each other and unrelated to the virus that causes warts, to treat warts, he did not at that time believe that other antigens unrelated to HPV, such as bacterial antigens, would also be effective to treat warts. And Dr. Horn has sworn in his declaration that he did believe at that time that any antigen, including bacterial antigens, that induced a cutaneous delayed type hypersensitivity reaction could be used to treat warts. Thus, the declaration establishes that Dr. Horn and his co-inventor, had conceived the use of any antigen or antigens that induce or are capable of inducing a cutaneous delayed type hypersensitivity reaction to treat common warts, including as is recited in the present claims, a bacterial antigen and a candida antigen.

The Examiner states that the "declaration must establish possession of either the whole invention claimed or something falling within the claim (such as a species of a claimed genus), in the sense that the claim as a whole reads on it," citing *In re Tanczyn*, 347 F.2d 830, 146 U.S.P.Q. 298 (C.C.P.A. 1965), and that Dr. Horn's declaration does neither (Office Action mailed Feb. 2, 2005). First, as argued above, Appellants contend that Dr. Horn's declaration does establish possession before the filing date of Bostwick of use of a bacterial antigen and a candida antigen to treat warts, where both antigens induce a DTH response, as well as any other antigen inducing a DTH response.

Furthermore, "Rule 131 requires applicant to make oath to facts showing completion 'of the invention.' That requirement does not mean affiant must show a reduction to practice of every embodiment of the invention." *In re Hostettler*, 356 F.2d 562 (C.C.P.A. 1966). The invention here is the use of an antigen to treat an epithelial tumor, such as warts, by injection into the epithelial tumor, where the antigen induces or is capable of inducing a cutaneous delayed type hypersensitivity (DTH) response. Dr. Horn's Declaration shows possession of that invention before the filing date of Bostwick.

The facts here show some parallels to those of *In re Stryker*, 435 F.2d 1340 (C.C.P.A. 1971). In *Stryker*, the applicant claimed a "process for removing polypropylene diluent from a suspension consisting essentially of from about 50%-60% by weight polypropylene . . ." *Id.* at 1340. The applicant attempted to remove a cited reference with a Rule 131 affidavit. The Board of Patent Appeals and Interferences held that the affidavit was deficient because it did not demonstrate possession of the particular weight percentages recited in the claim. *Id.* at 1341. The C.C.P.A. overturned the rejection. The C.C.P.A. first distinguished *Tanczyn*, the case also cited by the Examiner here, as concerning a situation where "the subject matter shown in [both] the reference and the affidavit was so different from the claimed invention that the claims were unobvious and patentable over the reference." *Id.* at 1341. The Court in *Stryker* then held:

> "To hold that Harban is not removed by the showing here presented would lead to an anomalous result, i.e., if appellant broadened his claims by deleting the weight limitations so as to read literally on Harban, Harban would not be available as a reference against such broadened claims because appellant's antedating affidavit would be satisfactory in every respect. It cannot be the law that the same affidavit is insufficient to remove the same reference applied against the slightly narrower claims presented here." *Id.* at 1341-1342.

The facts here are even stronger. The Examiner concedes that Dr. Horn's Declaration establishes possession of a pharmaceutical composition comprising a mumps antigen and a candida antigen. The originally filed claim 1, recited "A pharmaceutical composition for treating an epithelial tumor in a subject comprising at least two antigens and a pharmaceutically acceptable carrier, wherein each of said antigens induces or is capable of inducing a cutaneous delayed type hypersensitivity response in the subject." That originally filed claim 1 reads on the embodiment of the invention that the Examiner concedes Appellants possessed before the Bostwick filing date. But the Examiner required that Appellants narrow claim 1 in a restriction requirement to make searching easier. Now the Examiner rejects use of the Declaration to

remove Bostwick on the basis that the narrowed claim 1 no longer reads on the embodiment shown by the Declaration. The broader claim that would read on the embodiment shown by Dr. Horn's Declaration is, in fact, not just a hypothetical claim as was the case in *Stryker* but the originally filed claim 1 reciting a pharmaceutical composition comprising at least two antigens. This claim was narrowed to recite a pharmaceutical composition comprising a bacterial antigen and a candida antigen, solely in response to the Examiner's restriction requirement. To paraphrase the court in *Stryker*, it cannot be the law that the Examiner can demand that the claims be narrowed to make searching easier, and then assert that the Appellants' showing of possession with a Rule 131 Declaration, while it would have been sufficient to remove the reference with the original claims, is not sufficient with the narrower claims that the Examiner required in a restriction requirement.

Alternatively, Appellants' showing of a reduction to practice of a pharmaceutical composition comprising a mumps antigen and/or a candida antigen for treating warts establishes possession of a pharmaceutical composition comprising a bacterial antigen and a candida antigen for treating warts, wherein each of said antigens induces or is capable of inducing a cutaneous delayed type hypersensitivity response in a mammalian subject, because the latter composition is obvious in view of the former. This rule of obviousness in considering Rule 131 Declarations was elucidated in *In re Spiller* (500 F.2d 1170 (C.C.P.A. 1974)). *In re Spiller* is another case of an appeal from a rejection by the Board of an attempt with a Rule 131 Declaration to swear behind a cited reference. As in *Stryker*, the Board rejection was on the basis that the Declaration did not establish possession of all the limitations of the claims, and as in *Stryker* the C.C.P.A. overturned the Board decision. The C.C.P.A. held in *In re Spiller* that "for the purpose of antedating [a reference] under Rule 131, it is sufficient that appellant has shown a reduction to practice of his basic invention, which showing will also suffice as to claims differing therefrom only in details which are obvious to one of ordinary skill in the art." *In re Spiller*, at 1178.

Mumps antigen and candida antigen are both unrelated to the papilloma virus that causes common warts. They have little in common with each other besides the fact that both induce a delayed type hypersensitivity response in many human subjects because a large portion of the population has sensitivity to each. One antigen is viral and the other fungal. From those facts, which were known at the time of the Appellants' invention, it would have been obvious to one of ordinary skill in the art, in view of Appellants' invention of using mumps antigen and candida

antigen to treat warts, that any antigen which induces or is capable of inducing a delayed type hypersensitivity response could be used to treat warts.

Appellants' showing of a reduction to practice of a pharmaceutical composition comprising a mumps antigen and/or a candida antigen for treating warts renders obvious and thus establishes possession also of the presently claimed pharmaceutical composition comprising a bacterial antigen and a candida antigen for treating a benign epithelial tumor caused by a papilloma virus (e.g., warts), wherein each of said antigens induces or is capable of inducing a cutaneous delayed type hypersensitivity response in a mammalian subject.

Thus, the Rule 131 Declaration of Dr. Horn establishes possession of the invention before the filing date of Bostwick. First, Dr. Horn states in his Rule 131 Declaration that he conceived the use of any antigen, including a bacterial and candida antigen, that causes a cutaneous DTH response to treat warts before the filing date of Bostwick, and was diligent in developing the invention until the patent application was filed. This is supported by a letter from Dr. Fred Faas approving his use of candida and mumps antigens to treat warts in human patients dated before the filing date of Bostwick. This establishes possession of the presently claimed invention before the filing date of Bostwick.

If Dr. Horn's statement in his Rule 131 Declaration that he had conceived of use of a composition containing bacterial and candida antigens before the filing date of Bostwick is disbelieved or somehow discounted, it is still admitted by the Examiner that his Rule 131 Declaration establishes possession of a pharmaceutical composition comprising mumps and candida antigens to treat common warts. This falls within the scope of the originally filed claim 1 of the present application reciting "A pharmaceutical composition for treating an epithelial tumor in a subject comprising at least two antigens and a pharmaceutically acceptable carrier, wherein each of said antigens induces or is capable of inducing a cutaneous delayed type hypersensitivity response in the subject." It thus would suffice to establish possession of that claim and swear behind Bostwick if that claim had not been amended under the rule of *In re Tanczyn* (347 F.2d 830, 146 U.S.P.Q. 298 (C.C.P.A. 1965)) that the declaration overcomes the reference if it establishes possession of either the whole invention claimed or something falling within the claim (such as a species of a genus) in the sense that the claim as a whole reads on it (M.P.E.P. 715.02). But claim 1 was amended to recite a pharmaceutical composition comprising a bacterial antigen and a candida antigen solely in response to the Examiner's restriction

requirement to make the search easier. Under the rule of *In re Stryker*, the Examiner cannot demand that the claims be narrowed to make searching easier, and then assert that Appellants' showing of possession with a Rule 131 Declaration, while it would have been sufficient to remove the reference with the original claims is not sufficient with the narrower claims that the Examiner required in a restriction requirement.

Finally, even if both of those theories are rejected, Appellants' showing of a reduction to practice of a pharmaceutical composition comprising a mumps antigen and/or a candida antigen for treating warts establishes possession of a pharmaceutical composition comprising a bacterial antigen and a candida antigen for treating warts, wherein each of said antigens induces or is capable of inducing a cutaneous delayed type hypersensitivity response in a mammalian subject, because the latter composition is obvious in view of the former.

In all three of these ways, the Rule 131 Declaration of Dr. Horn establishes possession of the presently claimed invention before the filing date of Bostwick and removes Bostwick as a reference under 35 U.S.C. § 102(e). This obviates the rejection of the claims under 35 U.S.C. § 102(e) over Bostwick.

Issue b – Whether claims 1, 4-7, 33, 36-37, and 48-51 are anticipated under 35 U.S.C. 102(e) by Clements (U.S. Patent No. 6,033,673) under a theory of inherency.

Claims 1, 4-7, 33, 36-37, and 48-51 were rejected under 35 U.S.C. § 102(e) as anticipated by Clements (U.S. Patent No. 6,033,673, filed March 18, 1998). This rejection is respectfully traversed.

Inherency theory of rejection and burden of proof.

The rejection over Clements is based on a theory of inherency.

The pending claims recite "A pharmaceutical composition comprising at least two antigens and a pharmaceutically acceptable carrier, wherein (1) each of said antigens induces or is capable of inducing a cutaneous delayed type hypersensitivity response in a mammalian subject; (2) the composition is capable of treating a benign epithelial tumor caused by a papilloma virus in a mammalian subject; and (3) one of the two antigens is a bacterial antigen and the other is a candida antigen." The Examiner has noted, correctly, that the claims require that each antigen be capable of inducing a cutaneous DTH response in the pharmaceutical

composition, not on its own, free of the pharmaceutical composition (page 5 of Office Action mailed Feb. 2, 2005).

Clements discloses a novel mutant of *E. coli* heat labile enterotoxin modified by two amino acid substitutions and designated LT(R192G/L211A) (abstract). It discloses that the mutant enterotoxin can be administered in conjunction with any biologically relevant antigen or vaccine, such that an increased immune response to the antigen or vaccine is achieved (col. 9, lines 36-41). It discloses that the mutant enterotoxin and antigen can be administered simultaneously in a pharmaceutical composition (col. 9, lines 43-45). It discloses that many antigens may be used in the invention, including antigens from pathogenic fungi, and specifically including *Candida albicans* (col. 10, lines 27-29). It discloses that the mutant enterotoxin promotes the production of serum and/or mucosal antibodies as well as cell-mediated immune responses against antigens that are simultaneously administered with the mutant enterotoxin (col. 9, lines 6-10). It refers to the mutant enterotoxin as an adjuvant (abstract).

The Examiner asserts that Clements's disclosure of use of its specific *E. coli* mutant enterotoxin as an adjuvant in a pharmaceutical composition with specific antigens including *Candida albicans* constitutes disclosure of a pharmaceutical composition comprising a bacterial antigen and a candida antigen, wherein each antigen induces or is capable of inducing a cutaneous DTH response and the composition is capable of treating a benign epithelial tumor caused by a papilloma virus in a mammalian subject. But Clements says nothing about its composition treating a benign epithelial tumor, and it does not disclose that its *E. coli* mutant enterotoxin is an antigen at all in the pharmaceutical composition, or that it more specifically induces or is capable of inducing a cutaneous DTH response in the pharmaceutical composition disclosed. Thus, this reference can only anticipate the present claims if these traits are inherent traits of the composition disclosed in Clements. The Examiner apparently agrees, since he concedes that "the issues of inherency apply" (page 7 of the Office Action mailed May 31, 2005).

To rely on a theory of inherency to support a 35 U.S.C. § 102 rejection, the M.P.E.P. states that "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.P.E.P. § 2112, citing *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in the original). "[T]hat a certain result or

characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." M.P.E.P. 2112, citing *In re Rijckaert*, 9 F3d 1531, 1534 (Fed. Cir. 1993) (emphasis in the original).

In contradiction to this case law and statements in the M.P.E.P. on the burden of proof in making out a rejection on the basis that a characteristic is inherent in the prior art, the Examiner attempts to shift the burden to the Appellants to prove a negative. In the Office Action mailed February 2, 2005, the Examiner states without evidence or reasoning, "each of the antigens disclosed by Clements inherently induces or is capable of inducing a cutaneous delayed type hypersensitivity response. . . . In the absence of evidence the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences." (Office Action mailed February 2, 2005, pages 4-5.) First, the Examiner simply states without evidence or reasoning that inducing a DTH response is an inherent property of the mutant enterotoxin of Clements in the compositions of Clements, and then states that the burden is on the Appellants to prove otherwise. To support this burden shifting, he cites *In re Best,* 562 F.2d 1252 (C.C.P.A. 1977) and *Ex parte Gray,* 10 U.S.P.Q.2d 1922 (Bd. Pat. App. Int. 1989).

Both *In re Best* and *Ex parte Gray* concern claims that were functionally product-by-process claims and were evaluated under a product-by-process standard. Claim 1 in Best recited a crystalline zeolitic aluminosilicate having certain properties. *In re Best,* 562 F.2d at 1252. Claim 3 recited a process for preparing the product recited in claim 1. *In re Best,* 562 F.2d at 1253. The court cited a reference wherein

> [a]ll the positive process limitations are expressly disclosed except for the functionally expressed rate of cooling. However, there is nothing to indicate that this rate of cooling in any way differs from the normal rate resulting from removal of the heat source. Thus, the examiner's conclusion that those parameters of the resultant product which are recited in the appealed claims but are not expressly disclosed in the reference would be inherent is a reasonable one, absent convincing evidence to the contrary. *In re Best*, at 1254.

Ex parte Gray also involved claims evaluated as product-by-process claims. "While the present claims are drafted in the form of a compound or a composition, the rationale underlying appellants' arguments is founded on the proposition that the claims are directed to a product-by-process. In any event, we are convinced that the legal philosophy employed in rejections

involving products-by-process should be employed with respect to the claims before us." *Ex parte Gray*, 10 U.S.P.Q.2d at 1924.

The burden of proof for the Patent Office in making out a rejection for anticipation or obviousness of product-by-process claims is lower, according to the M.P.E.P. "The Patent Office bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims because of their peculiar nature." M.P.E.P. § 2113, quoting *In re Fessmann*, 489 F.2d 742, 744, 180 U.S.P.Q. 324, 326 (C.C.P.A. 1974).

Product-by-process claims are directed, typically, to a product that is nearly identical to a prior art product known to the inventors, differing only in the manner the product is produced. The differing method of production is alleged to create different properties in the product. Both *In re Best* and *Ex parte Gray* concerned products that were nearly identical to prior art products known to the inventors, but were prepared by a new process. *Ex parte Gray* concerned claims directed to human β nerve growth factor produced by recombinant means. *Ex parte Gray*, 10 U.S.P.Q.2d at 1923. The protein was already known, and the issue was whether producing the protein by recombinant means created a patentably distinct product. *In re Best* concerned a zeolitic aluminosilicate useful as a catalyst. *In re Best*, 562 F.2d at 1252. Similar zeolitic aluminosilicates useful as catalysts were already known. *Id.* at 1253. The claimed catalyst differed from the prior art catalysts only in the rate of cooling used to produce it. *Id.* at 1254. Where the only difference between a claimed product and a prior art product is the way it is produced, the board in *Ex parte Gray* and the court in *In re Best* have held that it is appropriate to shift the burden to the applicant to demonstrate that the different method of production creates a patentable difference in the product.

But the present claims are not product-by-process claims. So the lesser product-by-process standard is not appropriate. The appropriate standard is the standard for inherency rejections, as described above.

In the last Office Action, the Examiner quotes *In Re Best*, "the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable." (Page 6 of the final Office Action mailed May 31, 2005, emphasis added, quoting *In re Best* at 1252.) The Examiner is making Appellants' case: the question for the Board is whether the properties recited in the present claims are inherently present in the prior art. But again, to establish that the recited properties are inherently present in

the prior art and to substantiate a rejection on the basis of inherency, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the applied art." M.P.E.P. § 2112, citing *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. pat App. & Inter. 1990) (emphasis in the original).

Applying the standard for an inherency rejection to Clements and the present claims.

The question for the board is whether the composition disclosed in Clements containing the *E. coli* heat labile LT(R192G/L211A) mutant enterotoxin and an antigen, which may be a *Candida albicans* antigen, is necessarily a composition in which (1) the *E. coli* heat labile LT(R192G/L211A) is an antigen, (2) both the mutant enterotoxin and the *Candida albicans* antigen are antigens that induce or are capable of inducing a cutaneous DTH response in a mammalian subject in the composition disclosed, and (3) the composition is capable of treating a benign epithelial tumor caused by a papilloma virus in a mammalian subject. If the *E. coli* mutant enterotoxin when it is in the composition disclosed in Clements (1) is not necessarily an antigen, or (2) does not necessarily induce, or is not necessarily capable of inducing, a cutaneous DTH response, then Clements does not anticipate the present claims.

The *E. coli* mutant enterotoxin of Clements is not necessarily antigenic in the composition disclosed therein and is not necessarily capable of inducing a cutaneous DTH response in the composition disclosed therein because (1) not all proteins are antigenic in all compositions, (2) not all antigens are capable of inducing a DTH response, and (3) even those antigens that are capable of inducing a DTH response in some compositions may not induce the response in other compositions.

Clements describes its mutant *E. coli* enterotoxin as an adjuvant (abstract), not as an antigen. An adjuvant is "a vehicle used to enhance antigenicity, e.g., a suspension of minerals (alum, aluminum hydroxide, or phosphate) on which antigen is absorbed . . ." (Stedman's Medical Dictionary, 27th edition.) In contrast, an antigen is "[a]ny substance that, as a result of coming in contact with appropriate cells, induces a state of sensitivity and/or immune responsiveness after a latent period (days to weeks) and that reacts in a demonstrable way with antibodies and/or immune cells of the sensitized subject in vivo or in vitro." (Stedman's Medical Dictionary, 27th ed.) Thus, to be an antigen, a substance must induce an immune response

against itself. If it promotes an immune responses against another substance in the composition, it would be an adjuvant, which is how Clements describes the *E. coli* mutant enterotoxin, and not necessarily an antigen.

Not all proteins in all compositions are antigenic. Dr. Horn declares in the enclosed Declaration[1] under 37 C.F.R. § 1.132 executed 8/18/05, "[M]any foreign substances presented in certain compositions produce no immune response. The purpose of adjuvants such as Freund's complete adjuvant, is to enhance immune response to other potentially antigenic substances in the composition. Often an antigen can elicit a large immune response when presented with an adjuvant, but no detectable immune response when presented without an adjuvant. Thus, foreign substances that are potentially antigenic do not behave as antigens – that is, they do not induce an immune response – in certain formulations and with certain modes of presentation."

Even if a substance is antigenic in a particular composition, not all substances that are antigenic induce or are capable of inducing a cutaneous DTH response. Dr. Horn states in his Rule 132 Declaration: "[W]hen antigens do induce an immune response, the immune response can be in many forms, most of which are not a delayed type hypersensitivity response." This is evidenced not only by Dr. Horn's Rule 132 Declaration, but also by numerous statements in textbooks of immunology and in the published scientific literature. For instance, one textbook states: "A major question still remains as to the factors involved in determining whether cellular [e.g., a DTH response] or humoral immunity will develop in response to a certain antigen." (Nieuwenhuis, P., pp. 3-32, at page 27, in Marsh, J.A. et al. eds., *The Physiology of Immunity*, CRC Press, Boca Raton, FL, 1996.)

Dr. Horn cites two other published papers that show that not all antigens induce or are capable of inducing a DTH response in all compositions. Lichtenwalner et al., 2004, *Infection and Immunity*, 72:1159-1161, discloses testing several antigens from Chlamydia for induction of a delayed type hypersensitivity (DTH) response. Of the antigens, tested, only heat shock protein 60 induced a DTH response, while killed whole organisms, outer membrane protein, and heat shock protein 10 did not. To take another example, Shibata et al., 2001, *Infection and Immunity* 69:6123-6130, reports that immunization of mice with MPD-59 mycobacterial protein without

[1] The Rule 132 Declaration of Dr. Horn was not presented earlier because literature citations were relied upon to show that not all antigens induce or are capable of inducing a cutaneous DTH response in the Amendment filed March 5, 2005. The Examiner made the next Office Action final and indicated that Applicants' arguments based on

chitin induces certain immune response including IgE production and Th2 cells producing IL-4, IL-5, and IL-10, but does not induce Th1 cells or a delayed type hypersensitivity response (abstract). (Paragraph 7, Dr. Horn's Rule 132 Declaration.)

Thus, it is very clear that not all antigens induce or are capable of inducing a DTH response, especially not in all compositions. Furthermore, which antigens induce a DTH response cannot be predicted in advance, or the authors of the Lichtenwalner et al. and Shibita et al. papers would not have conducted their studies.

Clements discloses compositions containing a mutant enterotoxin and an antigen, and that administration of these compositions induces an immune response to the antigen (col. 9, lines 36-41). Clements does not disclose that any immune response directed to the mutant enterotoxin is generated. Much less does it disclose that specifically a cutaneous DTH response to the mutant enterotoxin is generated. Since not all antigens in all compositions induce a DTH response, and Clements does not disclose that any DTH response to the mutant enterotoxin of its compositions is generated, it is therefore not a necessarily inherent characteristic of the compositions disclosed in Clements that the mutant enterotoxin administered in those compositions induces or is capable of inducing a cutaneous DTH response against itself. Thus, Clements does not disclose a composition containing a candida antigen and a bacterial antigen, each of which induces or is capable of inducing a cutaneous delayed type hypersensitivity response in a mammalian subject.

Dependent claims 48-51

Even if the mutant enterotoxin of Clements were inherently an antigen that is capable of inducing a cutaneous DTH response in the compositions disclosed therein, claims 48-51 are still novel over Clements.

Clements discloses a new mutant *E. coli* enterotoxin molecule (column 6, lines 21-28). Since it is a new engineered molecule generated by site-directed mutagenesis (column 12, lines 59-61), no human or other mammal has been exposed to it and no human or other mammal would be expected to have a preexisting sensitivity to it. Thus, claims 48-49, reciting that humans have a preexisting sensitivity to each of the antigens such that each of the antigens, when injected intradermally into a human subject, induces a cutaneous delayed type hypersensitivity

published literature were attorney statements that are not evidence and must be supported by an appropriate affidavit or declaration (page 8 of the Office Action mailed May 31, 2005).

response in at least some human subjects (claim 48) or in most healthy human subjects (claim 49) are novel over Clements.

The Examiner has replied to this argument by stating that Clements discloses administration as boosters wherein the initial administration of the toxin and antigen is followed by a boost which may comprise the antigen alone or in combination with enterotoxin. (Final Office Action page 9, citing Clements column 9, lines 50-65.) This interpretation renders the limitation of preexisting sensitivity in claims 48 and 49 meaningless. If preexisting sensitivity to the presently claimed compositions exists where the compositions are first given to a subject to create preexisting sensitivity and then given as a booster, then the limitation is meaningless. Any antigenic composition can be given to a naive subject, never previously exposed to the antigen, to create sensitivity. But if the suggestion of administering an antigenic composition in a series of two or more injections constitutes preexisting sensitivity to the antigens contained in the composition, than the limitation is meaningless. All compositions containing antigens then are compositions containing antigens wherein humans have a preexisting sensitivity to each of said antigens. In order for the claim limitation to be a limitation at all, it must mean that humans have a preexisting sensitivity to the antigens before being exposed to the composition. Thus, this disclosure of Clements does not establish that the mutant enterotoxin of Clements is an antigen humans have a preexisting sensitivity to.

Claim 49 recites the pharmaceutical composition of claim 48 wherein each of said antigens induces a cutaneous delayed type hypersensitivity response in most healthy human subjects. Thus, this claim, depending on claim 48, includes the limitation of humans having a preexisting sensitivity to each of said antigens and the limitation that each of said antigens induces a cutaneous delayed type hypersensitivity response. Despite rejecting it, the Examiner did not comment on claim 49, but even if Clements' disclosure of administering its compositions as a boost constitutes "preexisting sensitivity" to the antigens, Clements does not suggest sensitizing most humans to its mutant enterotoxin, and so it would not be the case that the mutant enterotoxin induces a delayed type hypersensitivity response in most healthy human subjects.

Claim 50 recites the pharmaceutical composition of claim 1 wherein each of said antigens has a high prevalence of reactivity in humans or another mammal to induce a cutaneous delayed type hypersensitivity response. Again, since the enterotoxin adjuvant of Clements is a novel engineered molecule, it is not likely that humans or other mammals have a high prevalence of

reactivity to it. Furthermore, no evidence has been introduced that even wild type *E. coli* enterotoxin has a high prevalence of reactivity in humans or another mammal to induce a cutaneous delayed type hypersensitivity response. Thus, claim 50 also is novel over Clements. The Examiner offered no evidence or reasoning to rebut this argument for the patentability of claim 50 in the Final Office Action.

Claim 51 recites the pharmaceutical composition of claim 1 wherein each of said antigens is an antigen from a naturally occurring infectious agent. The enterotoxin of Clements is a new engineered molecule generated by site-directed mutagenesis (column 12, lines 59-61). Thus, it is not an antigen from a naturally occurring infectious agent. Again, this argument was raised previously, and the Examiner rejected this claim in the Final Office Action, but he offered no rationale for the rejection and no response to the argument.

Issue c – Whether claims 1, 4-7, 15, 33, 36-37, and 48-51 are obvious under 35 U.S.C. § 103(a) over Clements or Bostwick in further view of the Candin package insert.

Claims 1, 4-7, 33, 36-37, and 48-51 were rejected as obvious under 35 U.S.C. § 103(a) over Clements (U.S. Patent No. 6,033,673) or Bostwick (U.S. Published Patent Application 2002/0009429) in further view of the CANDIN® package insert. This rejection is respectfully traversed.

Bostwick is removed as prior art for the reasons argued under **Issue a** in this brief.

Three criteria must be met in order to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. M.P.E.P. § 2142, citing *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

With the removal of Bostwick as prior art by Dr. Horn's Rule 131 Declaration, as argued under **Issue a** in this brief, the rejection becomes a rejection over Clements in further view of the CANDIN® package insert.

The teachings of Clements and its deficiencies with respect to the present claims are discussed above under **Issue b**. Specifically, Clements discloses a composition containing the engineered *E. coli* heat labile LT(R192G/L211A) mutant enterotoxin and an antigen, which may be a *Candida albicans* antigen. But the mutant enterotoxin is not disclosed to be itself antigenic in the compositions. It is also not disclosed to induce or be capable of inducing a cutaneous DTH response in a mammalian subject in the compositions disclosed. It is well known and established by Dr. Horn's Rule 132 Declaration executed August 18, 2005, and by Lichtenwalner et al., 2004, *Infection and Immunity*, 72:1159-1161 and Shibata et al., 2001, *Infection and Immunity* 69:6123-6130, both cited in Dr. Horn's Declaration and above in this brief, and by Nieuwenhuis, cited above in this brief, that potentially antigenic substances may not be antigens in a particular composition, and if antigenic may not induce a delayed type hypersensitivity response. Accordingly, Clements does not disclose a composition that contains a candida antigen and a bacterial antigen, wherein each of said antigens induces or is capable of inducing a cutaneous DTH response in a mammalian subject, and wherein the composition is capable of treating a benign epithelial tumor caused by a papilloma virus in a mammalian subject.

Furthermore, Clements discloses its *E. coli* mutant enterotoxin is an adjuvant, not an antigen (abstract). Thus, it does not disclose or suggest the desirability of using the enterotoxin as an antigen – that is, of generating an immune response against the enterotoxin itself. Much less does it suggest the desirability of generating specifically a cutaneous DTH response to the enterotoxin. It also does not disclose or suggest that its compositions are capable of treating a benign epithelial tumor caused by a papilloma virus in a mammalian subject. Accordingly, Clements does not disclose or suggest all the elements of the presently claimed invention.

The CANDIN® package insert does nothing to remedy these deficiencies of Clements with respect to the present claims. The CANDIN® package insert describes the product as a Skin Test Antigen for Cellular Hypersensitivity made from the culture filtrate and cells of two strains of *Candida albicans*, a fungus (Description). It discloses it is indicated for use for detecting DTH by intracutaneous (intradermal) testing (Indications and Usage).

The CANDIN® package insert does not disclose or suggest combining the candida antigens with bacterial antigens that induce a cutaneous DTH response in a single pharmaceutical composition. It also does not disclose or suggest that the CANDIN®

composition or any other composition is capable of treating a benign epithelial tumor caused by a papilloma virus in a mammalian subject.

Thus, neither Clements or the CANDIN® package insert discloses or suggests combining a candida antigen and a bacterial antigen in a single pharmaceutical composition wherein both antigens induce or are capable of inducing a cutaneous DTH response in the compositions. Furthermore, neither discloses or suggests a composition that is capable of treating a benign epithelial tumor caused by a papilloma virus in a mammalian subject. Thus, the references do not teach or suggest all the elements of the present claims.

The references also provide no suggestion or motivation to modify the reference teachings to arrive at the presently claimed invention. The CANDIN® package insert discloses the existence of candida antigens and that they can be used to detect a cutaneous DTH response. Clements discloses use of a particular mutant *E. coli* enterotoxin as an adjuvant to enhance immune response to particular antigens. Clements discloses candida antigen as one antigen suitable for use in its compositions. Since Clements discloses the existence of the candida antigens, the CANDIN® package insert really adds nothing to the disclosure of Clements. Thus, the references do not provide a suggestion or motivation to modify reference teachings to arrive at the presently claimed invention.

Clements and the CANDIN® package insert also do not establish a reasonable expectation of success in creating a pharmaceutical composition comprising at least two antigens and a pharmaceutically acceptable carrier, wherein each of said antigens induces or is capable of inducing a cutaneous delayed type hypersensitivity response in a mammalian subject, the composition is capable of treating a benign epithelial tumor caused by a papilloma virus in a mammalian subject, and one of the two antigens is a bacterial antigen and the other is a candida antigen, because it was unknown until Appellants' invention that a composition containing a bacterial antigen and a candida antigen, wherein each of the antigens induces or is capable of inducing a cutaneous DTH response, could treat a benign epithelial tumor caused by a papilloma virus.

Accordingly, the combination of Clements and the CANDIN® package insert does not establish even one of the three requirements for a *prima facie* case of obviousness. Furthermore, the Examiner has not pointed to the particular features of Clements and the CANDIN® package insert that are alleged to establish a *prima facie* case of obviousness. The Examiner simply

makes conclusory statements such as "Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination," (page 10, Final Office Action mailed May 31, 2005) without pointing specifically to where all the elements of the present claims are taught in the two references, what teaching or suggestion is provided to combine or modify reference teachings, or what in the cited references establishes a reasonable likelihood of success of creating a composition that could treat a benign epithelial tumor caused by a papilloma virus.

For the reasons advanced above, Appellants respectfully contend that each claim is patentable. Therefore, reversal of all rejections is courteously solicited.

Respectfully submitted,

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Date _____ By:_____

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient first class postage, in an envelope addressed to: Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this ___ day of August 2006.

_____
Hugh McTavish

APPENDIX I

The Claims on Appeal

What is claimed is:

1. (Previously presented) A pharmaceutical composition comprising at least two antigens and a pharmaceutically acceptable carrier, wherein

each of said antigens induces or is capable of inducing a cutaneous delayed type hypersensitivity response in a mammalian subject;

the composition is capable of treating a benign epithelial tumor caused by a papilloma virus in a mammalian subject; and

one of the two antigens is a bacterial antigen and the other is a candida antigen.

2-3. Canceled.

4. (Previously presented) The pharmaceutical composition of claim 1 wherein the composition is capable of treating a benign epithelial tumor caused by a human papilloma virus in a human subject.

5. (Previously presented) The pharmaceutical composition of claim 1, wherein said benign epithelial tumor is a verruca, a condyloma, bowenoid papulosis, a laryngeal papilloma, or a epidermodysplasia verruciformis.

6. (Original) The pharmaceutical composition of claim 5, wherein said verruca is verruca vulgaris, verruca plantaris, verruca palmeris or verruca plana.

7. (Original) The pharmaceutical composition of claim 1, wherein said antigens are antigenic determinants, haptens or epitopes of said antigens and are responsible for inducing said delayed type hypersensitivity response in the subject.

8. Canceled.

9. (Withdrawn) The pharmaceutical composition of claim 1 wherein the composition further comprises a trichophyton antigen, a mumps antigen, or a combination thereof.

10. (Withdrawn) The pharmaceutical composition of claim 9, wherein said antigens are a combination of candida, trichophyton and mumps.

11. (Withdrawn) The pharmaceutical composition of claim 1, further comprising at least one cytokine or colony stimulating factor into said tumor.

12. (Withdrawn) The pharmaceutical composition of claim 11, wherein said colony stimulating factor is granulocyte macrophage colony stimulating factor and said cytokine is interferon-α, interferon-β, interferon-γ, interleukin-2 or interleukin-12.

13-14. Canceled.

15. (Original) A kit comprising at least one container, a hypodermic needle or a high pressure injection device, and the pharmaceutical composition of claim 1.

16. (Withdrawn) A kit of claim 15, further comprising at least one container, a hypodermic needle or a high pressure injection device comprising at least one additional pharmaceutical composition comprising at least one cytokine or colony stimulating factor into said tumor.

17. (Withdrawn) A kit comprising at least one container, a hypodermic needle or a high pressure injection device comprising the pharmaceutical composition of claim 11.

18-32. Canceled.

33. (Previously presented) The pharmaceutical composition of claim 1, wherein said pharmaceutical composition does not contain an immunogenic additive other than said antigens.

34-35. Canceled.

36. (Previously presented) The pharmaceutical composition of claim 1, wherein one of said antigens is an allergenic *Candida albicans* extract for intradermal testing.

37. (Previously presented) The pharmaceutical composition of claim 36, wherein said allergenic *Candida albicans* extract for intradermal testing is the *Candida albicans* Skin Test Antigen.

38-39. Canceled.

40. (Withdrawn) The pharmaceutical composition of claim 10, wherein said candida antigen is an allergenic *Candida albicans* extract for intradermal testing.

41. (Withdrawn) The pharmaceutical composition of claim 40, wherein said allergenic *Candida albicans* extract for intradermal testing is the *Candida albicans* Skin Test Antigen.

42-45. Canceled.

46. (Withdrawn) The pharmaceutical composition of claim 10, wherein said candida antigen is an allergenic *Candida albicans* extract, said mumps antigen is an allergenic Mumps Skin Test Antigen and said trichophyton antigen is an allergenic trichophyton extract.

47. (Withdrawn) The pharmaceutical composition of claim 46, wherein said allergenic *Candida albicans* extract for intradermal testing is the *Candida albicans* Skin Test Antigen.

48. (Previously presented) The pharmaceutical composition of claim 1 wherein humans have a preexisting sensitivity to each of said antigens such that each of said antigens, when injected intradermally into a human subject, induces a cutaneous delayed type hypersensitivity response in at least some human subjects.

49. (Previously presented) The pharmaceutical composition of claim 48 wherein each of said antigens induces a cutaneous delayed type hypersensitivity response in most healthy human subjects.

50. (Previously presented) The pharmaceutical composition of claim 1 wherein each of said antigens has a high prevalence of reactivity in humans or another mammal to induce a cutaneous delayed type hypersensitivity response.

51. (Previously presented) The pharmaceutical composition of claim 1 wherein each of said antigens is an antigen from a naturally occurring infectious agent.

APPENDIX II

Evidence Appendix

Clements, U.S. Patent No. 6,033,673. Cited in the Final Office Action mailed May 31, 2005.

Bostwick, U.S. Published Patent Application No 2002/009429. Cited in the Final Office Action mailed May 31, 2005.

CANDIN® Package Insert. Cited in the Final Office Action mailed May 31, 2005.

Nieuwenhuis, P., pp. 3-32, in Marsh, J.A. et al. eds., *The Physiology of Immunity*, CRC Press, Boca Raton, FL, 1996. Entered with the Amendment and Reply filed March 5, 2005.

Lichtenwalner et al., 2004, *Infection and Immunity*, 72:1159-1161. Submitted with the Appeal Brief filed August 24, 2005.

Shibata et al., 2001, *Infection and Immunity* 69:6123-6130. Submitted with the Appeal Brief filed August 24, 2005.

Definition of "Adjuvant," Stedman's Medical Dictionary, 27th edition, 2000, Lippincott, Williams & Wilkins, Philadelphia. Submitted with the Appeal Brief filed August 24, 2005.

Definition of "Antigen," Stedman's Medical Dictionary, 27th edition, 2000, Lippincott, Williams & Wilkins, Philadelphia. Entered with the Amendment and Reply filed March 5, 2005.

Declaration under 37 C.F.R. 1.132 by Dr. Thomas Dag Horn, dated 8/18/2005. Submitted with the Appeal Brief filed August 24, 2005.

APPENDIX III

Cases Cited

In re Tanczyn, 347 F.2d 830, 146 U.S.P.Q. 298 (C.C.P.A. 1965).

In re Hostettler, 356 F.2d 562 (C.C.P.A. 1966).

In re Stryker, 435 F.2d 1340 (C.C.P.A. 1971).

In re Spiller ,500 F.2d 1170 (C.C.P.A. 1974)).

Ex parte Levy, 17 U.S.P.Q.2d 1461 (Bd. Pat. App. & Inter. 1990)

In re Rijckaert, 9 F3d 1531 (Fed. Cir. 1993).

In re Best, 562 F.2d 1252 (C.C.P.A. 1977)

Ex parte Gray, 10 U.S.P.Q.2d 1922 (Bd. Pat. App. Int. 1989).

In re Fessmann, 489 F.2d 742, 180 U.S.P.Q. 324 (C.C.P.A. 1974).

In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

APPENDIX IV

Related Proceedings Appendix

None